Biochimica et Biophysica Acta 1822 (2012) 2–8

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Mast cells, angiogenesis, and tumour growth ☆

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ARTICLE INFO

Article history:
Received 25 June 2010
Received in revised form 8 October 2010
Accepted 24 November 2010
Available online 2 December 2010

Keywords:
Angiogenesis
Antiangiogenesis
Mast cells
Tumour growth

ABSTRACT

Accumulation of mast cells (MCs) in tumours was described by Ehrlich in his doctoral thesis. Since this early account, ample evidence has been provided highlighting participation of MCs to the inflammatory reaction that occurs in many clinical and experimental tumour settings. MCs are bone marrow-derived tissue-homing leukocytes that are endowed with a panoply of releasable mediators and surface receptors. These cells actively take part to innate and acquired immune reactions as well as to a series of fundamental functions such as angiogenesis, tissue repair, and tissue remodelling. The involvement of MCs in tumour development is debated. Although some evidence suggests that MCs can promote tumourigenesis and tumour progression, there are some clinical sets as well as experimental tumour models in which MCs seem to have functions that favour the host. One of the major issues linking MCs to cancer is the ability of these cells to release potent pro-angiogenic factors. This review will focus on the most recent acquisitions about this intriguing field of research. This article is part of a Special Issue entitled: Mast cells in inflammation.

1. Introduction

Mast cells (MCs) are bone marrow-derived tissue-homing leukocytes, which were first described more than 130 years ago by Paul Ehrlich in his doctoral thesis [1]. For many decades, these cells have represented a true enigma for researchers, being implicated in the pathogenesis of harmful, even lethal, allergic reactions and certain protective responses to parasites [2]. During the last years, however, a novel picture of their function has initiated to emerge, which has profoundly changed our perception of the biological significance and clinical implications of these cells. MCs, indeed, appear now as flexible, highly versatile tissue-related elements that play an important role in a large spectrum of biological settings, ranging from inflammation and immune modulation to angiogenesis, tissue repair, tissue remodelling, and cancer [3,4].

The complex and multifarious function of MCs in the field of tumour growth represents one of the most exciting frontiers in MC biology. The occurrence of a possible causative link between MCs, chronic inflammation, and cancer has long been suggested. As most tumours contain inflammatory cell infiltrates, which often include plentiful MCs, the question as to the possible contribution of MCs to tumour development has progressively attracted the attention of basic and clinical researchers [5–7]. These cells have the capacity to synthesize and release potent angiogenic compounds [8]. This is a major point linking MCs to cancer. However, the involvement of MCs in tumour promotion and expansion is complex and far from being settled. Although some evidence suggests that MCs can promote tumourigenesis and tumour progression, there are some clinical sets as well as experimental tumour models in which MCs seem to have functions that favour the host [9].

In this review article, the general biology of these cells will be firstly and shortly highlighted. Then the importance of angiogenesis in physiological and inflammatory conditions as well as in cancer will be discussed. Next, the specific contribution of MCs to angiogenesis in experimental tumours will be analyzed. Finally, the potential involvement of MCs in the development of solid and haematological tumours in different clinical settings will be debated.

2. Mast cell biology

In most histological sections, MCs appear as round or elongated cells with a diameter ranging between 8 and 20 μm. They are easily recognized by light microscopy for their plentiful toluidine blue-positive, metachromatic granules that fill the cytoplasm. MC granules represent the key functional cell organelles, whose content is extruded to the cell exterior upon cell activation in the form of either massive or limited degranulation. The former process is called exocytosis or anaphylactic degranulation while, for the latter, the term piecemeal degranulation has been coined [10,11]. As the name implies, anaphylactic degranulation is a generalized mode of granule release expressed by MCs during type I allergic reactions. By contrast, piecemeal degranulation appears as a discrete and selective pathway

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doi:10.1016/j.bbadis.2010.11.010

of cell secretion, which is a characteristic trait of MC activation in chronic inflammatory settings, like cancer for instance. In all species examined, MC granules contain a composite mixture of histamine (also serotonin in rodents), proteases, cytokines, and growth factors embedded in a glycosaminoglycan meshwork [12]. Besides the classical, toluidine blue secretory granules, MCs contain in their cytoplasm unique lipid bodies that are the source of arachidonic acid derivatives [11]. In addition, MCs express the tetrameric $\alpha\beta\gamma_2$ form of the high-affinity receptor FcεRI for immunoglobulin E (IgE) on their surface, which is crucial for the activation of the anaphylactic pathway of cell degranulation [13]. Thus, beyond a series of common features, MCs show marked differences in their phenotypic expression among diverse species and anatomical sites, a phenomenon called "MC heterogeneity" [14,15].

A milestone in our understanding of the biological profile of tissue MCs was the discovery that these cells originate from haematopoietic stem cells in the bone marrow, foetal liver, and cord blood. These progenitor cells circulate in the blood as non-granulated committed precursors [16–18]. Precursor cells migrate into different tissues in which they proliferate and differentiate into mature, granulated cells under the influence of several microenvironmental growth factors, in particular stem cell factor (SCF), the ligand for the c-kit tyrosine kinase III growth factor receptor (CD117) – secreted by fibroblasts, stromal cells and endothelial cells – which critically regulates many aspects of MC development and survival [19,20]. Development of tissue MCs is regulated also by interleukin (IL)-3, IL-4, IL-9, nerve growth factor (NGF), and probably other factors [21].

MCs display a distinctive pattern of cell distribution throughout the body. Such localizations enlighten us about some critical functions expressed by these cells. Two main districts are recognizable: (a) the body frontiers and (b) the connective tissues. MCs normally reside in proximity to surfaces that interface the external environment, i.e., the skin, mucosa of the gastrointestinal, respiratory, and genitourinary tracts, which are common portals of infection. Thus, MCs are likely to be among the first inflammatory cells to interact with invading pathogens [22]. MCs also populate the connective tissue structures near vessels and nerves, in a position that makes them key elements in processes like tissue remodelling, wound healing, fibrosis, and angiogenesis [23,24]. MCs have also been found in the central nervous system of several vertebrate species, where they provide putative functions that still await elucidation [25]. By contrast, MCs are not found in avascular tissues such as mineralized bone, cartilage, and the cornea.

MCs represent a rich source of biologically active mediators, which are either preformed in their granules or synthesized *de novo* [26,27]. The cross-linking of IgE with bivalent or multivalent antigens results in the aggregation of FcεRI, which is sufficient for initiating downstream signal transduction events that activate cell degranulation as well as the *de novo* synthesis and secretion of lipid mediators and cytokines [28]. Release of preformed and newly formed MC products from activated MCs leads to a series of profound biological effects. MCs may also be activated by "alternative", IgE-independent pathways, such as aggregation of FcγRIII by IgG/antigen complexes, c-kit and Toll-like receptor mechanisms, exposure to chemokines, anaphylatoxins C3a and C5a, fragments of fibrinogen and fibronectin [29–31].

MC mediators affect several aspects of inflammation and immune response, enabling these cells to act as important sentinels of the immune system. Thus, MCs are crucial cells in the initiation of both innate and acquired host defence against various pathogens. They are capable of recognizing, attaching to, phagocytosing, and directly killing a wide variety of opsonized Gram-negative and Gram-positive bacteria [32]. They recognize pathogens through pattern-recognition receptors (Toll-like receptors) and can respond with the induced expression of tumour necrosis factor (TNF)-α, type I interferons, and other inducible cytokines (IL-4, IL-6, IL-8) and chemotactic mediators (CCL3, CCL5, CXCL8) linked to the innate host response [31,33]. They also contribute to optimal initiation of acquired immunity by orchestrating migration, maturation, and function of dendritic cells and by interacting with T and B cells [34,35]. There are indications, however, that MCs may cause detrimental effects in virus infections by acting as a virus reservoir or helping viruses such as HIV-1, Dengue virus, cytomegalovirus, and adenovirus, by eluding immunosurveillance and hastening the inflammatory response [36]. *In vitro* experiments suggest that as MCs express MHC class I and II molecules, they can also act as antigen presenting cells and/or represent sources of co-stimulatory activity (e.g., by expressing CD40 or its ligand) [37].

MCs also affect tissue homeostasis, remodelling, repair, and fibrosis [38–40]. These functions are accomplished by a direct MC stimulation of specific connective tissue cell types, in particular fibroblasts, and by the release or activation of a series of extracellular matrix (ECM)-degrading enzymes. In addition, MCs synthesize and release many angiogenic growth factors, which exert important functions on blood and lymphatic vessel development.

Human MCs are conventionally divided into two types depending on the expression of different proteases in their granules and other functional features [41]. MCs, which contain tryptase only, are designated as MC_T or "immune cell associated" MCs. They are predominantly located in the respiratory and intestinal mucosa, where they co-localize around T lymphocytes. MCs that contain both tryptase and chymase, along with other proteases such as carboxypeptidase A and cathepsin G, are referred to as MC_{TC}. They are predominantly found in connective tissue areas, such as skin, submucosa of stomach and intestine, breast parenchyma, myocardium, lymph nodes, conjunctiva, and synovium. These two subsets of human MCs differ also in terms of their mediator content and reactivity. A third type of MC, called MC_C, has been identified. This MC expresses chymase without tryptase and resides mainly in the submucosa and mucosa of the stomach, small intestinal submucosa, and colonic mucosa [42].

3. The importance of angiogenesis in physiological and pathological conditions

Angiogenesis, i.e., the formation of new vessels from pre-existing ones – such as capillaries and post-capillary venules – plays a pivotal role during embryonic development [43]. Later, in adult life, angiogenesis occurs in several physiological (e.g., corpus luteum formation) and pathological conditions, such as tumour and chronic inflammation, where it may contribute to the progression of disease.

In 1971, Folkman published in the *New England Journal of Medicine* a hypothesis that tumour growth is angiogenesis-dependent and that inhibition of angiogenesis could be therapeutic [44]. This paper also introduced the term antiangiogenesis to mean the prevention of new vessel sprout from being recruited by a tumour. The hypothesis predicted that tumours would be unable to grow beyond a microscopic size of 1 to 2 mm^3 without continuous recruitment of new capillary blood vessels. Even if the majority of pre-clinical studies have shown that the growth of all experimental tumours can be effectively inhibited by various antiangiogenic agents, the clinical benefits of antiangiogenic treatments are relatively modest, and in the majority of cases, the drugs merely slow down tumour progression and prolong survival by only a few more months [45].

Under physiological conditions, angiogenesis is dependent on the balance of positive and negative modulators within the vascular microenvironment [46] and requires the functional activities of a number of molecules, including angiogenic factors, extracellular matrix proteins, adhesion receptors, and proteolytic enzymes. As a consequence, angiogenic endothelial cells have a distinct gene expression pattern that is characterized by a switch of the cell proteolytic balance towards an invasive phenotype as well as by the expression of specific adhesion molecules. In normal tissues, vascular

quiescence is maintained by the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli [47].

Pathological angiogenesis is linked to a switch in the balance between positive and negative regulators and mainly depends on the release by inflammatory or neoplastic cells of specific growth factors for endothelial cells that stimulate the growth of the host's blood vessels or the down-regulation of natural angiogenesis inhibitors [48].

Tumour blood vessels display many structural and functional abnormalities. They are irregular in size, shape, and branching pattern; lack the normal vessel hierarchy; and do not display the recognizable features of arterioles, capillaries, and venules [49]. Like normal blood vessels, they consist of endothelial cells, mural cells, and their enveloping basement membrane but each component of the vessel wall presents abnormalities. Tumour-associated endothelial cells proliferate 50–200 times faster than normal endothelial cells. They form a structurally defective endothelium, which shows discontinuities or gaps that allow haemorrhage and facilitate permeability of macromolecules and the traffic of tumour cells into the bloodstream. The basement membrane that envelops endothelial cells and pericytes of tumour vessels may have extra layers that have no apparent association with the cells. Pericytes of tumour vessels are loosely associated with endothelial cells, have abnormal shape, paradoxically extend cytoplasmic processes away from the vessel wall, and have extra layers of loosely fitting basement membrane. Thus, tumour vasculature is typically aberrant, disordered, and leaky.

4. The contribution of immune cells to angiogenesis in inflammation and tumour growth

There is increasing evidence to support the view that angiogenesis and inflammation are mutually dependent [50]. During inflammatory reactions, immune cells synthesize and secrete pro-angiogenic factors that promote neovascularization. On the other hand, the newly formed vascular supply contributes to the perpetuation of inflammation by promoting the migration of inflammatory cells to the site of inflammation [50]. The extracellular matrix and basement membrane are a source for endogenous angiogenesis inhibitors. On the other hand, many extracellular matrix molecules promote angiogenesis by stabilizing blood vessels and sequestering angiogenic molecules [51].

It is well established that tumour cells are able to secrete pro-angiogenic factors as well as mediators for inflammatory cells [48]. They produce indeed angiogenic cytokines, which are exported from tumour cells or mobilized from the extracellular matrix. As a consequence, tumour cells are surrounded by an infiltrate of inflammatory cells. These cells communicate via a complex network of intercellular signaling pathways, mediated by surface adhesion molecules, cytokines, and their receptors [52]. Immune cells cooperate and synergize with stromal cells as well as malignant cells in stimulating endothelial cell proliferation and blood vessel formation. These synergies may represent important mechanisms for tumour development and metastasis by providing efficient vascular supply and easy pathway to escape. Indeed, the most aggressive human cancers are associated with a dramatic host response composed of various immune cells, especially macrophages and MCs [50].

5. Mast cells and angiogenesis

MCs produce a large spectrum of pro-angiogenic factors. Human, rat, and mouse MCs release preformed fibroblast growth factor (FGF)-2 from their secretory granules [53,54]. Human cord blood-derived MCs release vascular endothelial growth factor (VEGF) upon stimulation through FcεRI and c-kit. Both FGF-2 and VEGF have also been identified by immunohistochemistry in mature MCs in human tissues [55,56]. Human MCs are a potent source of VEGF in the absence of degranulation through activation of the EP(2) receptor by PGE_2 [57]. Following IgE-dependent activation MCs released several pro-angiogenic mediators stored in their granules, such as VEGF [58] and FGF-2 [59], that promote angiogenesis even in the early phase of allergic inflammation. MCs can also migrate *in vivo* [60] and *in vitro* [61] in response to VEGF. Human lung MCs express VEGF-A, VEGF-B, VEGF-C, and VEGF-D at both mRNA and protein level. PGE_2 enhanced the expression of VEGF-A, VEGF-B, and VEGF-C, whereas an adenosine analog (5′-[*N*-ethylcarboxamido] adenosine [NECA]) increased VEGF-A, VEGF-C, and VEGF-D expression [62]. In addition, supernatants of PGE_2- and NECA-activated human lung MCs induced angiogenic response in the chorioallantoic membrane (CAM) assay that was inhibited by an anti-VEGF-A antibody. Finally, placental growth factor-1 induced MC chemotaxis [62].

Granulated MCs and their granules, but not degranulated MCs, are able indeed to stimulate an intense angiogenic reaction in the chick embryo CAM assay. This angiogenic activity is partly inhibited by anti-FGF-2 and -VEGF antibodies, suggesting that these cytokines are involved in the angiogenic reaction [63]. Similarly it has been demonstrated, using the rat-mesenteric window angiogenic assay, that intraperitoneal injection of compound 48/80 causes a vigorous angiogenic response [64]. The same treatment in mice also causes angiogenesis [65].

MCs store large amounts of preformed active serine proteases, such as tryptase and chymase, in their secretory granules [66]. Tryptase stimulates the proliferation of endothelial cells, promotes vascular tube formation in culture, and also degrades connective tissue matrix to provide space for neovascular growth. Tryptase also acts indirectly by activating latent matrix metallo-proteases (MMPs) and plasminogen activator (PA), which in turn degrade the extracellular connective tissue with consequent release of VEGF or FGF-2 from their matrix-bound state [67]. MC-derived chymase degrades extracellular matrix components, and therefore, matrix-bound VEGF could be potentially released.

Histamine and heparin stimulated proliferation of endothelial cells induced the formation of new blood vessels in the CAM assay [68,69]. Histamine stimulates new vessel formation by acting through both H1 and H2 receptors [69]. Heparin may act directly on blood vessels or indirectly by inducing release of FGF-2 from the extracellular storage site. In addition, other cytokines produced by MCs, such as IL-8 [70], TNF-α [71], transforming growth factor (TGF)-β, NGF [72], and urokinase-type PA have been implicated in normal and tumour-associated angiogenesis [73]. Lastly, MCs also contain preformed MMPs, such as MMP-2 and MMP-9, and TIMPs, which enable MCs to directly modulate extracellular matrix degradation. This, in turn, allows for tissue release of extracellular matrix-bound angiogenic factors.

6. Mast cell recruitment to tumour

It has recently been recognized that a condition of chronic inflammation stimulates proliferation of resident tissue MCs and promotes the local recruitment of circulating MC precursors [18,74]. This occurs during tumour development, whereby MCs form one of the major inflammatory cell populations and are now considered critical regulators of inflammation and the immunological response in the tumour microenvironment.

Huang and co-workers [75] were able to demonstrate that in a hepatocarcinoma model, MCs failed to migrate into SCF-knockdown tumours and anti-c-kit antibodies abolished the migration of MCs into tumours, leading to decreased tumour growth. This indicates that recruitment and activation of MCs in the tumour infiltrate are mainly mediated by tumour-derived SCF and its receptor c-kit on MCs. In the same experimental model, SCF stimulates the chemotactic migration of MCs. Some effects of SCF stimulation depend on the concentration of the cytokine. Low SCF concentrations induce the release of active MMP-9 into the local environment, while higher SCF concentrations promote activation in the tumour context of recruited MCs and the

release of proinflammatory factors such as IL-6, TNF-α, VEGF, Cox-2, i-NOS, and CCL-2 [75]. Activation of MCs by SCF has important consequences for tumour growth. Indeed, SCF-activated MCs in the tumour microenvironment increased the transcription of IL-17 gene and the amount of IL-17-producing cells in the tumour mass. In turn, IL-17 – a potential candidate for regulating the tumour inflammatory reaction through the production of IL-9 – would attract more MCs at the site of inflammation [76]. In addition, TNF-α and other proinflammatory factors released by MCs can increase the activity of NK-κB and AP-1 in tumour cells [75]. NK-κB and AP-1, in turn, may favour the proliferation of tumour cells by inducing the expression of cyclines, the surviving of tumour cells by the blockade of apoptosis, and the invasiveness of tumour cells by inducing the production of MIF and EMMPRIN [77,78].

7. Mast cells and tumour angiogenesis

An increased number of MCs have been reported in angiogenesis associated with vascular neoplasms, as well as a number of solid and haematological tumours [79]. Ehrlich was the first to find that MCs accumulate in tumours, especially carcinomas [80], but it was his pupil, Westphal, who recognized that MCs tended to gather at the periphery of carcinomatous nodules, rather than in the core of a tumour [81].

Experimentally induced tumours display MC accumulation close to the tumour cells before the onset of angiogenesis [82]. Likewise, an increase in MC number has been observed in tumour invasion around rat mammary adenocarcinoma [83]. Early studies in experimentally induced epidermoid carcinoma in hamster buccal pouches by repeated topical application of dimethylbenzanthracene demonstrated sequential MC migration towards progressive mucosal dysplasia and subsequent development of squamous cell carcinoma [84].

Development of squamous cell carcinoma in a human papilloma virus (HPV) 16- transgenic mouse model of epithelial carcinogenesis, obtained by transgenic expression of the early region of HPV type 16 in the basal cells of the squamous epithelium in transgenic mice using a human keratin 14 promoter, provided elegant experimental clues in favour of an early participation of MCs and MC-related angiogenesis in tumour growth [85]. Infiltration by MCs and activation of MMP-9 coincided with the angiogenic switch in premalignant lesions. MCs infiltrated hyperplasias, dysplasias, and the invasive front of carcinomas, but not the core of solid tumours, and were seen to degranulate in close apposition to capillaries and epithelial basement membranes, releasing tryptase and chymase. Remarkably, premalignant angiogenesis was abolished in a MC-deficient HPV16 transgenic mouse indicating that neoplastic progression in this model involved participation of MC infiltrating the skin.

It is generally accepted that most colon cancers develop from adenomatous polyps, and it has been demonstrated in mice that, from the onset, polyps are infiltrated with proinflammatory MCs and their precursors [86]. Depletion of MCs either pharmacologically or through the generation of chimeric mice with genetic lesions in MC development leads to a profound remission of existing polyps, suggesting that MCs are an essential haematopoietic component for preneoplastic polyp development as well as a possible target for therapeutic intervention.

In a pancreatic β-cell tumour model, activation of Myc *in vivo* has been shown to trigger rapid recruitment of MCs to the tumour site, recruitment that is absolutely required for macroscopic tumour expansion [87]. In addition, treatment of established β-cell tumours with cromolyn, an inhibitor of MC degranulation, rapidly triggers hypoxia and cell death of tumour and endothelial cells. Similarly, activation of Myc in β-cells of genetically MC-deprived mice does not elicit any measurable β-cell or islet expansion.

Experimental evidence indicates that angiopoietin-1 (Ang-1) secreted by primary murine MCs promotes marked neovascularization in an *in vivo* transplantation assay [88]. Primary MCs accelerate tumour growth by established plasmacytoma cell lines and the use of Ang-1-neutralizing antibodies reduces significantly the growth of plasmacytomas containing MCs.

In tumours, MCs are recruited and activated via several factors secreted by tumour cells. One of the most important is the SCF [89,90]. Besides the SCF, other MC-recruiting and/or -activating factors have been identified, namely FGF-2, VEGF, platelet-derived endothelial cell growth factor (PD-ECGF), RANTES and monocyte chemotactic protein (MCP)-1, adenosine, and adrenomedullin [91–93].

Association between MCs and new vessel formation has been reported in breast cancer [94,95], colorectal cancer [96], and uterine cervix cancer [97]. Tryptase-positive MCs increase in number and vascularization increases in a linear fashion from dysplasia to invasive cancer of the uterine cervix [98]. An association of VEGF and MCs with angiogenesis has been demonstrated in laryngeal carcinoma [99] and in small lung carcinoma, where most intratumoural MCs express VEGF [100–102]. MC accumulation has also been noted repeatedly around melanomas, especially invasive melanoma [103,104]. MC accumulation was correlated with increased neovascularization, MC expression of VEGF [105] and FGF-2 [106], tumour aggressiveness, and poor prognosis. Indeed, a prognostic significance has been attributed to MCs and microvascular density not only in melanoma [107] but also in squamous cell cancer of the oesophagus [108]. Recently, angiogenesis has been shown to correlate with tryptase-positive MC count in human endometrial cancer. Both parameters were found to increase in agreement with tumour progression [109].

MC density, new vessel rate, and clinical prognosis have also been found to correlate in haematological tumours. In benign lymphadenopathies and B cell non-Hodgkin's lymphomas, angiogenesis correlates with total and tryptase-positive MC counts, and both increase in step with the increase with malignancy grades [110,111]. In non-Hodgkin's lymphomas, a correlation has been found between vessel count and the number of MCs and VEGF-expressing cells [112]. In the bone marrow of patients with inactive and active multiple myeloma as well as those with monoclonal gammopathies of undetermined significance, angiogenesis highly correlates with MC counts [113]. A similar pattern of correlation between bone marrow microvessel count, total and tryptase-positive MC density and tumour progression has been found in patients with myelodysplastic syndrome [114] and B cell chronic lymphocytic leukemia [115]. In the early stages of B cell chronic lymphocytic leukemia, the density of tryptase-positive MCs in the bone marrow has been shown to predict the outcome of the disease [116].

8. Conclusions

MCs appear as important elements in tumour development and progression. Their early recruitment in the tumour microenvironment and the multifarious functions they are able to express justify the increasing interest these cells have been attracting in this field of research. The literature is rich of investigations on MC engagement in different tumour settings. Data, however, are somewhat contradictory, and MC effects on tumour fate have been described as either positive or negative, depending upon the different clinical or experimental context. Indeed, correlation between their number and prognosis in various human tumour types shows some discrepancies, which are recognizable also in experimental studies of carcinogenesis.

Literature data converge in indicating MCs as a key source of angiogenic and tissue remodelling factors in the tumour milieu. This appears as a primary contribution of MCs to tumour development. But it is not the only one (Fig. 1). Once recruited in the tumour context, MCs may either play additional roles by attracting other inflammatory cells or, alternatively, suppress anti-tumoural responses. MCs, indeed,

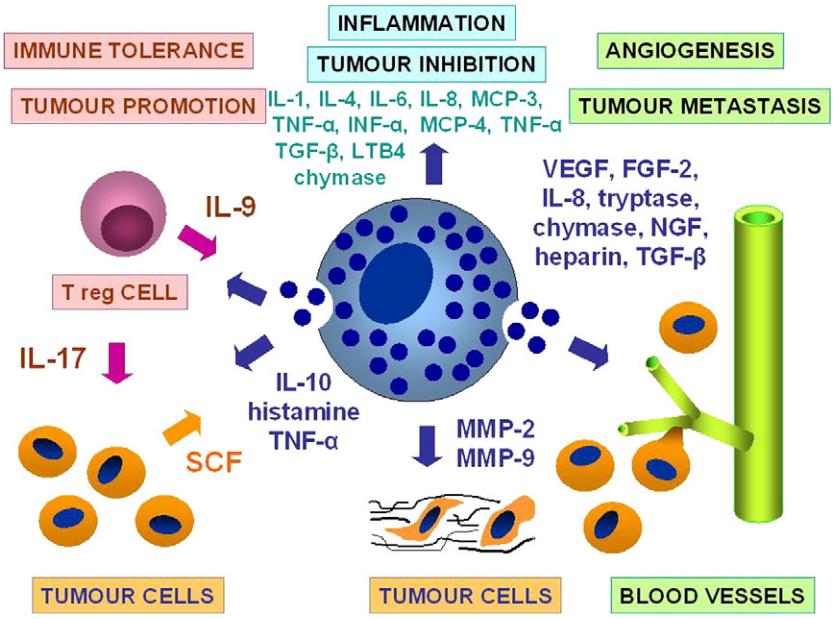

Fig. 1. Drawing illustrating the complex role of MCs in the tumour scenario. Mast cells attracted in the tumour context by SCF secreted by tumour cells produce several angiogenic factors – such as VEGF, FGF-2, IL-8, tryptase, chymase, NGF, heparin, and TGF-β – as well as matrix metallo-proteases, like MMP-2 and MMP-9, which promote tumor vascularization and tumor invasiveness, respectively. MCs may also generate immunosuppression by releasing IL-10, histamine, and TNF-α. MCs infiltrating the tumor stroma favour expansion and activation of regulatory T cells (T reg cells), which, in turn, stimulate immune tolerance and tumor promotion. By contrast, MCs may promote inflammation, inhibition of tumor cell growth, and tumor cell apoptosis by releasing cytokines such as IL-1, IL-4, IL-6, IL-8, MCP-3, MCP-4, INF-α, TNF-α, TGF-β, LTB4, and chymase. TNF-α, in particular, is very effective in leukocyte chemoattraction. Abbreviations: SCF, stem cell factor; VEGF, vascular endothelial growth factor; IL-8, interleukin-8; FGF-2, fibroblast growth factor-2; NGF, nerve growth factor; TGF-β, transforming growth factor-β; MMP-2, MMP-9, matrix metallo-protease 2, -9; MCP-3, MCP-4, mast cell protease-3, -4; TNF-α, tumor necrosis factor-α; INF-α, interferon-α; LTB_4, leukotriene B4.

have been found to be capable of suppressing immune reactions [117]. These cells not only produce inhibitory cytokines, such as IL-10 [118], but also are essential in promoting the immune tolerance mediated by regulatory T (Treg) cells. Indeed, MCs serve as enforcers for Treg cells, turning down the immune system's reaction to skin allograft possibly by IL-10 secretion [119]. Thus, the pivotal role of MCs in the induction of an acquired condition of immune tolerance may be critical for sustaining tumour growth.

The potential implication of MCs in tumour biology has stimulated the production of drugs or experimental procedures leading to MC depletion or inhibition of MC secretion. Indeed, MCs might act as a new target for the adjuvant treatment of tumours through the selective inhibition of angiogenesis, tissue remodelling and tumour-promoting molecules, permitting the secretion of cytotoxic cytokines and preventing MC-mediated immune suppression. Preliminary studies using anti-c-kit antibodies [75], anti-TNF-α antibodies [120], or the MC stabilizer disodium cromoglycate (cromolyn) [121] in mouse models have demonstrated promising results even if administered after the initiation of tumour development. Further studies will hopefully shed light on these important aspects of MC biology.

Acknowledgments

This study was supported in part by MIUR (PRIN 2007), Rome, and Fondazione Cassa di Risparmio di Puglia, Bari, Italy.

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